Assessing Animal Models of Bacterial Pneumonia Used in Investigational New Drug Applications for the Treatment of Bacterial Pneumonia

Ursula Waack, MS, PhD
Oak Ridge Institute of Research and Education
OID/OND/CDER
No disclosures/conflicts of interest

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.
Animal Models Used in Early Drug Development

Nonclinical Development

- **in vitro studies**
- **in vivo studies**
- PK/PD Studies
- Safety/Toxicology
- Proof-of-Concept

Clinical Development

- Phase I/II/III
IND Database

- INDs submitted to Division of Anti-Infectives since Jan. 1, 2000

  - Search terms: pneumonia or bacterial infection
    - *No tuberculosis, cystic fibrosis, or biothreats*

  - 27 INDs, 180 studies

Published Studies Database

- Search PubMed with
  - “Animal model pneumonia antibacterial”
  - January 1, 2000 to December 31, 2019

- Literature with pneumonia model
  - *No tuberculosis, cystic fibrosis, or biothreats*
  - Treatment after bacterial inoculation
  - No co-infection with virus (*i.e.* influenzae strain)

  - Study not included in IND database
    - Removed 22 studies

  - 137 papers, 377 studies
Trend towards using more Gram-Negative bacteria in IND studies
Bacteria in Published Studies

Gram-Negative
- Acinetobacter baumannii
- Acinetobacter lwoffii
- Burkholderia cenocepacia
- Chlamydia pneumoniae
- Chlamydia trachomatis
- Enterobacter cloacae
- Escherichia coli
- Haemophilus influenzae
- Haemophilus parainfluenzae
- Klebsiella pneumoniae
- Legionella pneumophila
- Mycoplasma pneumonia
- Mycobacterium abscessus
- Pasteurella multocida
- Pseudomonas aeruginosa

Gram-Positive
- Streptococcus pneumoniae
- Staphylococcus aureus
- Co-infection
Murine Models Predominately Used

IND Database (n=180)

Published Studies Database (n=377)

*No ventilator-associated pneumonia models in IND database
Mice used for shorter studies

* hpi: hours post infection
Bacterial Load Most Common Endpoint

IND Database
- Bacterial Load: 94.4%
- Dose for 50% Survival: 2.8%
- Survival: 2.8%
Total=180

Published Literature Database
- Bacterial Load: 82.5%
- Dose for 50% Survival: 16.7%
- Survival: 0.8%
Total=377

Legend:
- Blue: Bacterial Load
- Red: Dose for 50% Survival
- Green: Survival
Similar Use of Neutropenic and Immunocompetent Models

IND Database

- Neutropenic: 0 studies
- Immunocompetent: 24 studies

Published Literature Database

- Neutropenic: 2 studies
- Immunocompetent: 69 studies
- Unknown: 2 studies

Legend:
- Orange: Aerosol
- Blue: Intrabronchial
- Red: Intranasal
- Green: Intratracheal
- Purple: Oral
- Black: Unknown
Conclusions

• Study designs are highly variable
  – Opportunity for harmonization

• IND database and Published Literature database are distinct datasets that show similar trends
  – Surprisingly, little overlap exists between the databases
Conclusions, continued

• Both neutropenic and immunocompetent animals were used in models

• Studies with neutropenic mice inoculated intranasally were most common

• Mice were utilized for short term studies (<48 hours), larger animals for longer term studies (>48 hours)
Acknowledgments

• John Farley, MD
• Edward Weinstein, MD, PhD
• Thushi Amini, PhD
• Simone Shurland, PhD
• Abhay Joshi, PhD
• James Byrne
• Stephen Bart, PhD

• Oak Ridge Institute of Science and Education (ORISE)
Similar use of Neutropenic and Immunocompetent Mice for Predominant Bacteria in INDs
Similar use of Neutropenic and Immunocompetent Mice for Predominant Bacteria in Published Literature